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**CHALLENGE** TB



# Challenge TB Core Bedaquiline Coordination Project

*Year 2 Annual Report*  
*July 1, 2015 – September 30, 2016*

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**Cover photo:** Nurmaya (shown on left), a 36-year old, was initially diagnosed with tuberculosis (TB) in a private health facility in 2013. However, she discontinued treatment after nine months. Six months later she fell ill again and restarted TB treatment with another private doctor. In 2016, after one year of treatment and with no improvement, she was referred to a public hospital, where she was diagnosed with multidrug-resistant tuberculosis (MDR-TB) and started treatment for MDR-TB. However, three months later, she was found to have resistance to additional anti-TB drugs. She was then started on a bedaquiline (Bdq) containing treatment regimen in September 2016. Here she is shown in conversation with Mrs Nurul (shown on right), Pharmacovigilance (PV) Officer, Ministry of Health (MoH), Indonesia.

Photo credit: Trishanty Rondonuwu, KNCV Indonesia Country Office.

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## List of Abbreviations and Acronyms

aDSM	Active tuberculosis drug-safety monitoring and management
AE	Adverse event(s)
APA	Annual Plan of Activities
ATS	American Thoracic Society
Bdq	Bedaquiline
CAP	Compassionate Access Programme
CTB	Challenge TB
Dlm	Delamanid
DR	Drug resistance
DR-TB	Drug resistant tuberculosis
DST	Drug susceptibility testing
EMA	European Medicines Agency
FQ	Fluoroquinolone(s)
GDF	Global Drug Facility
KNCV	KNCV Tuberculosis Foundation
LTTA	Long term technical assistance
MDR-TB	Multidrug resistant tuberculosis
M&E	Monitoring and evaluation
MoH	Ministry of Health
MSF	Medecins Sans Frontieres
MSH	Management Sciences for Health
ND&R	New drugs and regimens
NTP	National TB control Programme
OR	Operational Research
PATH	Program for Appropriate Technology in Health
PMDT	Programmatic management of drug resistant tuberculosis
PV	Pharmacovigilance
SIAPS	Systems for Improved Access to Pharmaceuticals and Services Program
rGLC	regional Green Light Committee
R&R	Recording and reporting
RR-TB	Rifampicin resistant tuberculosis
SL	Second line
SLD	Second line drug(s)
SLI	Second-line injectable(s)
SOP	Standard Operating Procedures
STR	Shorter MDR-TB treatment regimen
STTA	Short term technical assistance
TA	Technical Assistance
TB	Tuberculosis
USAID	United States Agency for International Development
WHO	World Health Organization
XDR-TB	Extensively drug resistant TB

## Executive Summary

The Challenge TB (CTB) *Core Bedaquiline Coordination Project* (hereafter termed the *Core Project*) facilitates the introduction of new drugs and shorter regimens (ND&R) in the twenty-two CTB supported countries, in accordance with local legal frameworks and based on the principle of “**Right Diagnosis, Right Treatment**”. With the United States Agency for International Development (USAID) leading overall global coordination, the *Core Project* support team (KNCV Tuberculosis Foundation [KNCV] and Systems for Improved Access to Pharmaceuticals and Services Program [SIAPS]) facilitates, coordinates and monitors the *Core Project* implementation in all CTB countries to ensure a consistent approach and comprehensive scale up. Each partner’s collaboration is imperative to reach a common approach and understanding, communicate consistent messaging and avoid duplication of work.

In year one of the *Core Project*, the support team developed: (1) an implementation planning tool that is intuitive and user-friendly; and (2) a generic programmatic & clinical guide based on the KNCV-developed ‘Patient Triage Concept’. Through a series of workshops, CTB introduced the ND&R concept to all CTB coalition partners and countries in April and June of 2016, and in a CTB coalition partner-led workshop in August of 2016. During these workshops, the ‘Implementation Planning Tool for the Introduction of ND&R’ and ‘Generic programmatic and clinical guide’ were used to identify the gaps to successful ND&R introduction. The foundation for successful ND&R implementation is centered on a strong programmatic management of drug resistant tuberculosis (PMDT) component of the respective National TB Control Programme (NTP). Comprehensive introduction of ND&R is complex, requiring careful revision to the management of drug resistant tuberculosis (DR-TB) patients and necessarily goes beyond the replacement or addition of a single drug in a treatment regimen.

The *Core Project’s* team has addressed challenges to successful ND&R implementation through high level advocacy at the Ministry of Health (MoH), adaptation of national diagnostic algorithms and treatment regimens, support for drug supply chain management as well as strengthening of in-country partnerships for active drug-safety monitoring and management (aDSM) to ensure patient safety. The latter included the introduction of necessary monitoring tests, training and the establishment of electronic systems for data collection and analysis.

The *Core Project* has already achieved distribution of the CTB generic tool and guide to all CTB countries since their recent completion. In addition, tool adaptation was already achieved in several countries (Indonesia, Kyrgyzstan, Nigeria, Tajikistan, Ukraine, and Vietnam), while continued adaptation is on-going in several other countries (Botswana, DR Congo, Mozambique, and Uzbekistan).

Encountered challenges in the introduction of ND&R across the twenty-two CTB countries have been highly country specific and not unexpected. To start, many of the basic PMDT requirements were found not to be in place. These ‘missing’ essential components varied from a partial or complete lack of commitment to introduce ND&R to a lack of required laboratory capacity and/or associated human resource issues and inadequate pharmacovigilance (PV) systems, including aDSM. Recording and reporting (R&R) systems were also often found to be either not in place or inadequate, further complicated by issues around drug procurement and supply management. The lack of registration of drugs is yet another problem often encountered.

By the end of September 2016, thirteen countries had developed their country specific strategic documents, and 489 patients had been enrolled on a regimen containing Bdq (Table 1). As noted, countries are currently in different stages of preparation. Countries like Botswana, Nigeria, Ukraine and Uzbekistan are adapting generic guides, calculating drug needs, ensuring basic safety monitoring measures and plan to start enrollment in the first semester of 2017. Other countries like Kyrgyzstan and Tajikistan are ready for ND&R to be introduced after gaining approval from the MoH, with staff having been trained in early diagnosis, treatment initiation and monitoring of treatment safety and efficacy. They are ready to introduce ND&R and will start patient enrollment by the end of 2016.

By the end of 2017, countries will report on planned enrollment of over 3,200 patients on Bdq-containing treatment regimens (in at least seventeen countries) as well as over 3,400 patients on the STR (in at least seventeen countries), with CTB support under country APA3 work plans (Table 1).

Table 1. Summary of patient data

	<b>By end of Sept 2016</b>	<i>By end of Dec 2016</i>	<i>By end of Dec 2017</i>
<b>Number (#) of patients (pts) enrolled on Bdq containing regimens by end of Sept 2016</b> <i># of pts planned to be enrolled on Bdq containing regimens by end of Dec 2016 and by end of Dec 2017</i>	<b>489</b>	<i>1,098</i>	<i>3,255</i>
<b># of pts enrolled on Dlm containing regimens by end of Sept 2016</b> <i># of pts planned to be enrolled on Dlm containing regimens by end of Dec 2016 and by end of Dec 2017</i>	<b>32</b>	<i>129</i>	<i>365</i>
<b># of pts enrolled on STR by end of Sept 2016</b> <i># of pts planned to be enrolled on STR by end of Dec 2016 and by end of Dec 2017</i>	<b>464</b>	<i>1,097</i>	<i>3,410</i>

# Introduction

Bedaquiline (Bdq) and delamanid (Dlm) are the first new tuberculosis (TB) drugs developed in more than 40 years. Both drugs have been approved by stringent national drug regulatory authorities (Bdq by the US Food and Drug Administration and the European Medicines Agency [EMA], Dlm by the EMA and the Pharmaceuticals and Medical Devices Agency of Japan). The World Health Organization (WHO) has included Bdq and Dlm in its Essential Medicines List. The WHO has published interim policy guidance on the use of Dlm and Bdq in adult multidrug resistant TB patients (MDR-TB: TB resistant to rifampicin and isoniazid), and very recently on the use of Dlm in children and adolescents with MDR-TB. Both drugs, when used per WHO guidance and in combination with existing medications, provide new hope for DR-TB patients currently with limited treatment options.

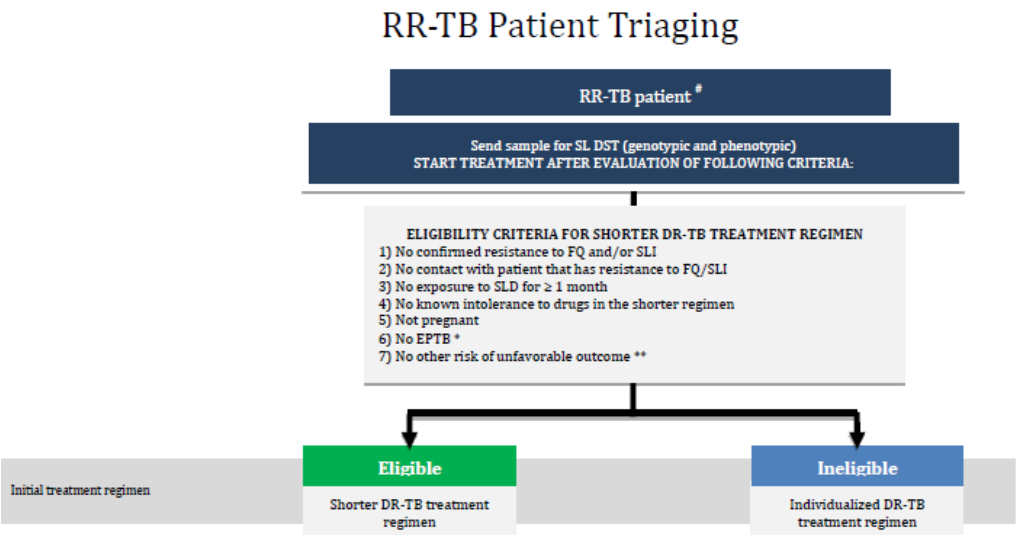
USAID launched a Bdq donation program for the treatment of MDR-TB patients in April 2015, which will provide 30,000 Bdq treatment courses to patients in more than 100 countries. In addition, USAID committed to provide technical assistance (TA) to both countries and programs. Bdq and Dlm (from March 2016) are available through the Stop TB Partnership’s Global Drug Facility (GDF) for all countries that are Global Fund eligible.

The *Core Project* was developed to facilitate the introduction of ND&R in CTB supported countries, with the overall objective of coordination, monitoring, and provision of support to the introduction of ND&R in these countries. During the year one of the project implementation, WHO issued updated guidelines on management of DR-TB (May 2016) recommending the use of rapid molecular tests for early detection of resistance to key second line drugs (SLD) and programmatic introduction of a shorter MDR-TB treatment regimen (STR).

As introduction of the STR and the new drugs are directly linked, the project provided support for implementation of both innovations, under the KNCV-developed ‘Patient Triage Approach’ (

**Figure 1 ‘Patient Triage Approach’ for RR-/MDR-TB patients** <https://www.kncvtbc.org/en/what-we-do/the-kncv-patient-triage-concept/>). The implementation of appropriate diagnostic and treatment algorithms allow for early allocation of the best DR-TB treatment regimen to rifampicin-resistant tuberculosis (RR-TB) and MDR-TB patients when additional resistance to SLDs is detected or suspected. Patients without resistance to second-line injectable (SLI) and/or fluoroquinolones (FQ) are allocated to the STR. Patients with extensive resistance to SLD will be allocated to a conventional length treatment (20-24 months) regimen, with the addition of new and/or repurposed drugs to the regimen.

Figure 1 ‘Patient Triage Approach’ for RR-/MDR-TB patients





## Progress by Objective/Sub-objective

**Challenge TB intervention area.** 3.2. Access to quality treatment and care ensured for TB, DR-TB and TB/HIV for all risk groups from all care providers.

The specific objectives, sub-objectives and intervention area under the CTB Project are as follows:

**Objective.** Improved access to quality patient centered care for TB, TB/HIV and MDR-TB services.

**Sub-Objective.** 3.2.3 Patient-centered and treatment.

**The following four main activities were implemented:**

1. Development of tools to guide introduction of ND&R in all CTB countries

During year one of the *Core Project*, the support team developed: i. an intuitive and user-friendly implementation planning tool for the introduction of ND&R; and ii. a generic programmatic and clinical guide to facilitate the introduction of ND&R by the CTB supported countries, guided by the overarching principle of “**Right diagnosis, Right treatment**”, based on the KNCV-developed Patient Triage Concept.

- Implementation Planning Tool for the Introduction of ND&R (Annex 2 Generic Implementation Planning Tool for the introduction of ND&R)

This tool assists the introduction of ND&Rs by highlighting the gaps in the existing processes, TA needs, and development of operational plans. It leads the user through a detailed breakdown of the required activities from the introductory steps to national scale-up, with tentative timelines for each step and set of activities. These activities are to be done in parallel, and there is no need for all of the elements to be in place nationally, prior to the enrolment of the first patients at a treatment site.

Elements of the tool include:

i. National level: a) Awareness & political engagement; and b) Update national PMDT strategy for ND&R.  
ii. Treatment site level (per site): a) Planning; b) Monitoring and Evaluation (M&E) framework; c) Diagnosis; d) Treatment initiation; e) Monitoring of treatment response; f) aDSM; g) Capacity building; and h) Drug management.

- Generic Programmatic and Clinical Guide for the Introduction of ND&R (Figure 2. and Annex 3 Generic Programmatic and Clinical Guide for the introduction of ND&R)

The generic guide is complementary to the ‘Implementation Planning Tool for the introduction of ND&R’ and is based on WHO guidelines, the endTB Project Guide on New Drugs, and Medecins Sans Frontieres (MSF), The UNION and Global Drug Resistant Initiative protocols for the STR. This document describes the steps necessary to implement the STR and the new drugs for DR-TB treatment, including diagnosis and bacterial confirmation of drug resistance (DR), treatment regimen design, monitoring of treatment efficacy and safety, and programmatic evaluation. These steps are detailed within an MDR-TB/extensively drug resistant-TB (XDR-TB) ‘Patient Triaging Approach’. The guide can be downloaded from the CTB website at <https://www.challengeb.org/library>

This approach entails:

- a) Availability of DR test results (and periodic test results to monitor treatment) based on optimized diagnostic algorithms for early detection of RR-TB and resistance to FQ and SLI. Algorithms should be adapted over time when new diagnostic tests become available;
- b) Provision of treatment regimens for RR-TB patients depending on the additional resistance detected or suspected and/or intolerance to either FQ and/or SLI in compliance with WHO recommendations;
- c) Routine data collection on patients diagnosed with RR-TB in accordance with WHO guidelines on PMDT, new drugs, and aDSM guidelines;

- d) Patient management before, during and after treatment in accordance with WHO guidelines on PMDT and WHO guidelines on the introduction of new drugs; and
- e) Monitoring and supervision visits to support high-quality programmatic implementation of the MDR-/XDR-TB 'Patient Triaging Approach'.

**Figure 2 Generic Programmatic and Clinical Guide for the Introduction of ND&R**



The *Core Project* has distributed these CTB generic tools to all CTB countries since their recent completion. Tool adaptation has been achieved in several countries (Indonesia, Kyrgyzstan, Nigeria, Tajikistan, Ukraine, and Vietnam), while continued adaptation is on-going in several other countries (Botswana, DR Congo, Mozambique, and Uzbekistan).

## 2. Intensive support to priority countries with programmatic introduction and/or scale-up of ND&R, as well as generating evidence supporting the scale-up

- To facilitate the CTB Annual Plan of Activities in year three (APA3) planning cycle and possible adjustments to APA2 Quarters 3 and 4 implementations, a “CTB Core Bedaquiline Coordination Project Workshop” took place with the CTB coalition and partners in The Hague, The Netherlands, from March 31st to April 1st 2016. The aim of the workshop was to ensure a coordinated, efficient and effective approach towards the introduction of Bdq in CTB project countries, making best use of resources and the joint experiences of the CTB coalition partners. The workshop was attended by a representative from USAID, Washington DC, USA and representatives from seven members of the CTB Coalition (American Thoracic Society (ATS), Interactive Research and Development, KNCV, Management Sciences for Health [MSH]/SIAPS, Program for Appropriate Technology in Health [PATH], The Union and WHO). In addition to the sharing of experiences, the participants laid out a clear set of next steps to be completed in the subsequent months, including planning a workshop for CTB country teams in June 2016 prior to the Country Directors’ meeting week in The Hague, The Netherlands (see following bullet point).
- The CTB ‘Implementation Planning Tool for the Introduction of ND&R’ and the ‘Generic programmatic and clinical guide’ were introduced and used during a series of workshops. The first workshop, held in The Hague, The Netherlands in June 2016, was attended by the technical staff from the CTB coalition partners’ country offices, representatives from CTB partners’ central offices, and CTB country Technical Focal Points from KNCV Central Office. A follow-on workshop held in August 2016 in Delhi, India, and organized by The Union’s South

East Asian Regional Office and with CTB supported TA, brought together over sixty participants including representatives of the NTPs and CTB in-country technical staff from Bangladesh, India, Indonesia, Myanmar and Nepal, and representatives. From both workshops, the gaps that were required to be filled prior to introduction of ND&R and the next steps to address the gaps were identified, and draft work plans (both national and APA3 related) were started on, or existing plans updated, for the introduction of the ND&R in the respective countries.

- Via CTB supported TA, by the end of September 2016, thirteen countries developed their country specific strategy documents for the introduction of ND&R (See Table 3. – baseline at start of APA2 was just one country had such a document which required updating). In addition, five countries were assisted in developing their country specific programmatic and clinical guide to facilitate the introduction of ND&R using the generic CTB guide (baseline at start of APA2 was two countries). This included development of country specific diagnostic algorithm, regimen design, aDSM and monitoring framework.
- As virtually all the CTB countries were in the early stages of preparation for the introduction of ND&R, than monitoring visits of ND&R activities, STTA was provided to assist the countries prepare for the introduction of ND&R. 48 Missions to 15 countries (see Annex 5 for details) were conducted, with 44 funded from CTB country project funds, and 1 from core project funding. The areas of work included: to a DR surveillance survey (in Zimbabwe); assessment of existing DR-TB situation and PMDT services (e.g. Botswana, Cambodia, DR Congo, Kazakhstan, Mozambique, Nigeria, Ukraine, and Uzbekistan); support to development of second line (SL) drug susceptibility testing (DST) services (in Burma and Cambodia); facilitation of workshops for ND&R introduction, including for aDSM (e.g. in Kyrgyzstan, Nigeria, Tajikistan, and a regional workshop in India involving Bangladesh, Burma, India, Indonesia and Nepal); and support to preparatory work for the introduction of ND&R, including development of programmatic and clinical guide, and implementation activities (e.g. to Burma, Cambodia, India, Kyrgyzstan, Nigeria, Tajikistan, Tanzania, Ukraine, Vietnam). Further details are provided in
- **Annex 5 CTB supported LT-/STTA visits**



Annex 5. Additional  
TA missions.docx

- .
- The *Core Project's* team systematically documented progress in countries, with at least thirteen countries having introduced Bdq containing regimens via various sources of support, including CTB (Table 2. and **Annex 4 Patients data**). The baseline number was nine countries - however only two of these had patients enrolled on treatment under programmatic conditions. The remainder had patients under treatment either under compassionate use programmes or individual patient care. The total baseline number of patients on Bdq-containing regimens under these various sources was likely to be less than 50). By the end of September 2016, 489 patients have been enrolled on a Bdq containing regimen.
- Following advocacy work in June 2016 during the ND&R workshop and the CTB Country Directors meeting in The Hague, The Netherlands, many of the approved country APA3 work plans are anticipated to include specific activities to support further the introduction of ND&R in the respective countries.

### 3. Support introduction of ND&R in countries by complementing funding or providing TA for areas not budgeted in the country work-plans

- A separate work plan proposal under the *Core* project, developed by the KNCV Central Asia Regional Office staff, to support Bdq introduction in Kazakhstan by the NTP using the *Core project* funding, was approved in June 2016. Field assessments of two Oblasts (Regions) were undertaken in August 2016 with a report and draft plan for the national roll out of treatment regimens containing new drugs, submitted in October 2016.

**Table 2. Patient data by CTB country**

	Number (#) of patients (pts) enrolled by end of Sept 2016			# of pts planned to be enrolled by end of Dec 2016			# of pts planned to be enrolled by end of Dec 2017		
	Bdq containing regimens	Dlm containing regimens	STR	Bdq containing regimens	Dlm containing regimens	STR	Bdq containing regimens	Dlm containing regimens	STR
Afghanistan	<b>Not Applicable (NA)</b>	<b>NA</b>	<b>NA</b>	NA	NA	NA	Not Known (NK)	NK	NK
Bangladesh	<b>33</b>	<b>0</b>	<b>83</b>	56	30	200	120	94	1110
Botswana	<b>Not Available (NAv)</b>	<b>NAv</b>	<b>NAv</b>	NAv	NAv	Nav	25	2	NK
Burma	<b>7</b>	<b>3</b>	<b>0</b>	20	10	0	20	10	200
Cambodia	<b>0</b>	<b>0</b>	<b>0</b>	0	0	0	1	1	30
CAR Kazakhstan	<b>145</b>	<b>26</b>	<b>NA</b>	270	50	NA	307	150	NK
CAR Kyrgyzstan	<b>0</b>	<b>0</b>	<b>0</b>	20	0	35	67	30	200
CAR Tajikistan	<b>13</b>	<b>0</b>	<b>0</b>	63	1	100	50	NA	100
CAR Uzbekistan	<b>120</b>	<b>0</b>	<b>146</b>	180	0	146	320	0	100
DR Congo	<b>2</b>	<b>NA</b>	<b>125</b>	10	NA	394	25	NA	696
Ethiopia	<b>7</b>	<b>2</b>	<b>NA</b>	42	25	0	48	29	NK
India	<b>56</b>	<b>0</b>	<b>0</b>	150	0	0	1600	0	0
Indonesia	<b>44</b>	<b>NAv</b>	<b>NAv</b>	100	NAv	Nav	200	20	300
Malawi	<b>NA</b>	<b>NA</b>	<b>NA</b>	0	0	0	To Be Advised (TBA)	TBA	TBA
Mozambique	<b>7</b>	<b>0</b>	<b>42</b>	119	10	102	20	NK	144
Namibia	<b>10</b>	<b>1</b>	<b>0</b>	15	3	20	50	13	170
Nigeria	<b>NA</b>	<b>NA</b>	<b>NA</b>	NA	NA	NA	16	16	288
South Sudan	<b>NA</b>	<b>NA</b>	<b>NA</b>	NA	NA	NA	NK	NK	NK
Tanzania	<b>1</b>	<b>NA</b>	<b>0</b>	1	NA	0	36	0	72
Ukraine	<b>0</b>	<b>0</b>	<b>0</b>	0	0	0	250	NK	NK
Vietnam	<b>44</b>	<b>NA</b>	<b>68</b>	50	NA	100	100	NK	NK
Zimbabwe	<b>NA</b>	<b>0</b>	<b>0</b>	2	0	0	TBA	TBA	TBA
<b>TOTALS</b>	<b>489</b>	<b>32</b>	<b>464</b>	1,098	129	1,097	3,255	365	3,410

## Conclusions

In year one of the *Core Project*, CTB Generic tools and guide for the introduction of ND&R have been developed, shared with all CTB countries and already adapted in several countries (Indonesia, Kyrgyzstan, Nigeria, Tajikistan, Ukraine, and Vietnam), whilst the adaptation process continues in other countries (Botswana, DR Congo, Mozambique, and Uzbekistan).

Comprehensive introduction of ND&R is complex, requiring careful revision to the management of DR-TB patients and necessarily goes beyond the replacement or addition of a single drug in a treatment regimen. Comprehensive preparatory work is needed to ensure quality of patient care, adequate safety and efficacy monitoring with basic PMDT elements in place. This begins with early assessments and the development of strategies on how to introduce new drugs and regimens through the NTPs. The Core Project's team has addressed challenges to successful ND&R implementation through high level advocacy at the MoH level, adaptation of national diagnostic algorithms and treatment regimens, support for drug supply chain management as well as strengthening in-country partnerships for aDSM to ensure patient safety. The latter included the introduction of necessary monitoring tests, training and the establishment of electronic systems for data collection and analysis.

The CTB countries are in distinct and different stages of the preparatory process. Countries like Botswana, Nigeria, Ukraine, and Uzbekistan are adapting the generic guide, calculating drug needs, establishing basic safety monitoring measures etc., and plan to start enrollment in first six months of 2017. Other countries like Kyrgyzstan and Tajikistan are ready to introduce new drugs and regimens upon gaining approval from the MoH and having trained the staff in early diagnosis, early treatment initiation and monitoring of treatment safety and efficacy. Patient enrollment will start by the end of 2016 in these two countries. Overall by the end of September 2016, thirteen countries had developed their country specific strategic documents, and 489 patients had been enrolled on a regimen containing bedaquiline.

**Table 3. Project achievements against agreed APA 2 milestones**

Planned Key Activities for the Current Year	Activity #	Planned Milestones				Milestone status	Milestone met?	Remarks
		Oct-Dec 2015	Jan-Mar 2016	Apr-Jun 2016	Year end	Oct 2015 – September 2016		
Development of detailed strategy per CTB country	<b>1</b>	2 countries	4 countries (planned to include Tajikistan, Nigeria)	6 countries (planned to include Kazakhstan, Botswana, DR Congo)	8 countries (planned to include Ethiopia, Burma)	13 countries have strategies developed (Bangladesh, Burma/ Myanmar, DR Congo, Ethiopia, India [Bdq only], Indonesia, Kyrgyzstan, Nigeria, Tajikistan, Tanzania, Ukraine, Uzbekistan, and Vietnam). 13 countries (Bangladesh, Burma / Myanmar, DR Congo, Ethiopia, India, Indonesia, Kazakhstan, Mozambique, Namibia, Tajikistan, Tanzania, Uzbekistan and Vietnam) are enrolling patients on Bdq containing regimens (under CTB, endTB Project, and other sources – see Annex 4)	<b>Met</b>	CTB TA funded though CTB country budgets – awaiting approval of continued TA included in APA3 workplans
Development of generic training modules, to be used in all countries	<b>2</b>	Drafts ready: based on inventory and CTB / SIAPS developed modules	Full set ready: development of additionally required modules	Dissemination of training modules to CTB partners. Use of training modules in countries ready to start using new drugs and regimens (Kyrgyzstan,	Use of training modules in other countries ready to start using new drugs and regimens (to be determined)	eModule on new drugs and regimens developed.  Materials developed for an ND&R related training held in Kyrgyzstan in July 2016.  Local materials already developed in Tajikistan.  NTP in Burma/Myanmar is currently using training modules and tools from the endTB project.	<b>Partially met</b>	eModule on new drugs and regimens to be used and evaluated.  Development and finalization of further material to be done under APA3 as needed.

Planned Key Activities for the Current Year	Activity #	Planned Milestones				Milestone status	Milestone met?	Remarks
		Oct-Dec 2015	Jan-Mar 2016	Apr-Jun 2016	Year end	Oct 2015 – September 2016		
				Ukraine, Tajikistan)		<p>India has developed training modules for the Bdq Compassionate Access Programme (CAP) in place, with CTB TA. NTP plans to revise existing training modules to incorporate elements on ND&amp;R, and CTB will provide TA to the process.</p> <p>Tanzania: Training material for ND&amp;R near finalization. PV training package/standard operating procedures (SOP) will soon be developed.</p>		
Development of generic materials and protocols, to be adjusted per country	<b>3</b>	Draft ready: Development draft generic protocol	Full set ready: Share generic protocol and materials with partners for comments and finalize	Capacity building of regional Green Light Committees (rGLC) and others	Continued updating generic materials base  Capacity building rGLCs and others	<p>Generic programmatic and clinical guide, and planning tool for the introduction of ND&amp;Rs finalized (work led by KNCV). Work on electronic PV recording system and Pharmaco- Vigilance Monitoring System ongoing (led by SIAPS).</p> <p>Several countries have developed their country specific materials and protocols (India, Tajikistan, Tanzania), others are awaiting approval (Kyrgyzstan, Ukraine), or are currently using endTB project guidelines whilst planning to</p>	<b>Partially met</b>	<p>Generic programmatic and clinical guide, and planning tool for the introduction of ND&amp;Rs to be widely disseminated and used by countries under APA3.</p> <p>Country specific TA to be continued in APA3 to facilitate further development and approval of country specific documents.</p>

Planned Key Activities for the Current Year	Activity #	Planned Milestones				Milestone status	Milestone met?	Remarks
		Oct-Dec 2015	Jan-Mar 2016	Apr-Jun 2016	Year end	Oct 2015 – September 2016		
			Orientation / capacity building CTB partners			develop their own programmatic guidelines (Burma / Myanmar).		
Coordination with USAID/SIAPS/CTB partners and support data collection for evidence related to ND&R introduction	4	CTB partners appointed focal points for Bdq TA Core Project	All CTB Focal Points have up to date information on the project - identify needs for capacity building on ND&R introduction among CTB partners - partners familiar with project M&E  Integration of qualitative M&E on ND&R implementation into the CTB management system	Data collection	Data collection	CTB staff from 15 countries and 2 regional staff, and representatives from 4 CTB partners' central offices (ATS, MSH, The Union and WHO), updated on current relevant policies, and project documents at a CTB workshop for the introduction of ND&R, in The Hague, The Netherlands, in June 2016.  On-going collaboration across partners in a few CTB countries in relation to collection of relevant data.  KNCV is piloting an interim (bridging) database in a few countries (Kyrgyzstan, Uzbekistan) whilst the overall electronic recording and reporting systems are being developed and introduced. SIAPS will support implementation of the QUANTB tool.	<b>Partially met</b>	Ongoing discussions with all coalition partners and their respective country teams to prioritize the area of work, preferably through reprogramming of APA2 funding and inclusion in draft APA3 work plans.

Planned Key Activities for the Current Year	Activity #	Planned Milestones				Milestone status	Milestone met?	Remarks
		Oct-Dec 2015	Jan-Mar 2016	Apr-Jun 2016	Year end	Oct 2015 – September 2016		
Additional support visits from HQ to Challenge TB countries when needed	5	1 country	3 countries	4 countries	5 countries	48 Missions to 15 countries (see Annex 5 for details) were conducted. 44 missions were funded from country project funds, and 1 from core project funding.	<b>Met</b>	

## Key Challenges and Actions

The challenges faced during year one of the *Core Project* implementation for the introduction of ND&R across the twenty-two CTB supported countries were highly country specific and not unexpected, ranging from problems arising from a lack of political commitment to the practical time required to develop plans. Preliminary analyses highlighted the wide differences between the respective CTB countries in their stage of implementation. On the ground, it was found that many of the essential PMDT components were either partially or totally absent because of a lack of focus on PMDT by NTPs previously, especially in the low MDR-TB burden countries. From late 2015 onwards, new requirements specifying the need of aDSM for ND&R (with the progressive scale-up to cover all MDR-TB patients in time) resulted in all countries not having this component in place, even those with more mature PMDT activities. In addition, the new drugs are registered only in a limited number of countries. Many the challenges faced are more of a global level issue and advocacy at that level is required for resolution of the issue.

### Common technical challenges faced by many countries included:

Countries	Key challenges
<b>i. Lack of commitment to introduce ND&amp;Rs</b>	
Cambodia	Obtaining NTP agreement to introduce ND&R has been a challenge whilst there are still large stocks available of the drugs used in the previous MDR-TB treatment regimens.
India	Dlm is not yet registered.
Kyrgyzstan	Insufficient funds to cover the needs.
<i>Actions to overcome challenges</i>	Advocacy and awareness raising activities undertaken with the appropriate levels.
<b>ii. Lack of required laboratory capacity</b>	
Tanzania	Limited availability to SL line probe assay test.
India	Sputum collection and transportation networks remain a challenge.
<i>Actions to overcome challenges</i>	Provision of appropriate TA to build local capacity. Advocacy and awareness raising activities undertaken with the appropriate levels.
<b>iii. Health workforce related issues</b>	
India and Tanzania	Lack of awareness and knowledge of Health Care Workers in relation to ND&R.
Cambodia	Limited human resources capacity.
Indonesia	High turnover of PV Officers at implementing sites, need time to be (re-)trained.
Tajikistan	Tools (e.g. clinical protocols) for the treatment of DR-TB patients with ND&R not available.
<i>Actions to overcome challenges</i>	Provision of appropriate TA to build local capacity, including support to the development and/or revision of existing training material, to work-load analyses leading to the optimal utilization of the existing staff, and development and finalization of clinical protocols (including need for translation into local languages).
<b>iv. Inadequate PV systems, including Adsm</b>	
Tanzania	Inadequate PV systems in place. aDSM a novel concept, with no or minimal systems in place.
Indonesia	Shift from passive PV processes to an active one (i.e. aDSM), needs time to be taken on board and implemented.
India	Further strengthening of the aDSM mechanism and managing information flow among the different involved agencies required.
<i>Actions to overcome challenges</i>	Provision of appropriate TA to build local capacity and local systems, including support the strengthening of the links between the existing PV agencies and NTPs.
<b>v. Inadequate R&amp;R systems in place</b>	
Tanzania	Inadequate R&R system posed risks to the planning of activities and drug quantification. Introduction of electronic systems are essential.
Nigeria, Kazakhstan and Bangladesh	Existing systems sub-optimal for planning of drug quantification and ordering.

Countries	Key challenges
Indonesia	Not all patients who qualify for Bdq-containing treatment were contacted partly due to long turnaround times in delivering of test results (and limitations in contacting eligible patients related to distance from health care facilities).
<i>Actions to overcome challenges</i>	Provision of appropriate TA to build local capacity and local systems, including support to strengthening the functioning of currently implemented systems for drug quantification e.g. QUAN TB.
<b>vi. Drug procurement chain and supply management issues</b>	
All countries	<p>Bdq and Dlm are registered only in a limited number of countries. Hence the drugs are not registered in the clear majority of the CTB-supported countries. And even in those countries where registration has happened, access to the new drugs is only allowed via very limited channels. For example, in India, access to Bdq is restricted via just the six treatment sites working under the NTP. Some countries will not entertain any request for licensing for any new drug that does not have Phase III trial data. Many others either have antiquated regulations regarding compassionate use or expanded access programme use or no regulations. This is the case also for some of the companion drugs, however the situation differs across the various countries.</p> <p>In addition, local drug procurement regulations can also lead to further delays in drug delivery time. For example, in Namibia, the local drug procurement regulations stipulate that drugs can only be procured by the government using a competitive bidding process (tenders) and payment after delivery of service. This bureaucratic process of getting pre-payment for shipment of Bdq caused significant delays. However, an emergency shipment was negotiated with GDF.</p>
<i>Actions to overcome challenges</i>	Work with all stakeholders, both NTPs and international (GDF, Partners In Health, MSF) to support the development of mechanisms which allow access to the new drugs both in the short term (e.g. via waivers for drug importations) and longer term (full licensing).
All countries	<p>Long lead time.</p> <p>Theoretical time from drug order until drug arrival at a central warehouse via GDF is six months. Generally, however it takes seven-nine months or longer.</p> <p>Short drug self-life of Bdq (two years).</p> <p>This means less than fifteen months of effective self-life once the drug is received at a central warehouse.</p>
<i>Actions to overcome challenges</i>	Work with global level stakeholders to advocate for better drug delivery mechanisms for example via GDF and at the respective drug manufacturer to ensure a longer shelf life for Bdq.

## Lessons Learnt / Next Steps

Introducing ND&R is only one of the components in a complex management package requiring a solid PMDT foundation. Long term TA (LTTA) and short term TA (STTA) provides the opportunity to strengthen the essential country setting components of PMDT, with strong support from the national level (administrative, political and technical support). Essential steps for ND&R introduction need to be clearly defined which will be helpful to synchronize the necessary activities. Partners' respective roles and responsibilities in the introduction of ND&R must be defined as one of the initial steps. Preparatory activities to the initial implementing sites for patients' enrollment on treatment are to be executed in parallel with national level strategic discussions and advocacy efforts.

However, some of the essential steps took significantly longer than was envisioned initially, as legal framework issues and systemic challenges needed to be addressed country-wide. Experience has shown that there needs to be one to two years of platform strengthening for a country's preparedness to introduce or accelerate patient enrollment. Capacity should be in place at the individual, organizational and institutional levels. For example, in Kyrgyzstan, the challenges encountered with the drug procurement order and drug delivery resulted in a delay of patient enrolment.

### Country specific examples

Country	Preparatory activities conducted	Next steps
Kyrgyzstan	Advocacy work resulted in support from MoH	Patient enrollment by the end of 2016; Subsequent expansion to other treatment sites
	New drugs included in national guidelines	
	National plan for ND&R developed and endorsed by MoH	
	Triage approach and proposed regimens supported by WHO, rGLC, MSF, Defeat TB experts	
	Adverse event (AE) monitoring within MDR-TB program was revised and link with PV authority strengthened	
Nigeria	Advocacy work resulted in support from MoH	Drug procurement; Training of staff in pilot sites; Patient enrollment in Q1-2 2017
	Draft National plan for ND&R developed	
	Generic CTB guide adapted	
Tajikistan	Advocacy work resulted in support from MoH	Patient enrollment by the end of 2016; Subsequent expansion to other treatment sites
	National plan for ND&R developed and endorsed by MoH	
	Triage approach and proposed regimens supported by WHO, rGLC, MSF, Defeat TB experts	
	AE monitoring within MDR-TB program was revised and link with PV authority strengthened	

To reach the Core Project's objective and to enable sustainable active country participation and ownership, it is essential to continue to support countries through STTAs on proper implementation and scale of activities and to continue monitoring the countries progress to provide a consistent approach. Long term- TA and STTA, supportive supervision and clinical mentoring visits to both KNCV led and non-KNCV led CTB countries will need to be conducted through country level funds when available. Such visits will support the country to develop the required plans and

documents, to troubleshoot implementation issues, and ensure a high-quality ND&R introduction. Furthermore, such visits will provide good insights on cross cutting implementation opportunities and challenges that can be shared with other CTB countries. A key activity to be supported through CTB APA3 work plans, is for each CTB country to develop, or update, a country specific operational plan for the introduction or scale-up of ND&R, utilizing the generic tools developed under APA2.

Regular interaction between KNCV consultants in the Central Office in The Hague, technical experts of the other CTB coalition partners, and in-country teams, for example via bimonthly teleconferences and webinars, will be established to build local capacity to accelerate the introduction of ND&R in the respective countries. Monthly calls will be established with the in-country CTB PMDT Focal Point / Technical Officers to be briefed on the country progress (including review of the latest data collected), to understand current issues and gaps in implementation, and plan appropriate action.

The *Core Project's* team will systematically document progress in countries and monitor and evaluate evidence data collected through APA2 and APA3. A momentum has been built at the country level in relation to the introduction of ND&R. In addition, development, finalization and dissemination of the *Core Project's* generic documents and tools will be supported through the *Core Project* to become widely used public domain documents. During APA3, the *Core Project's* team will finalize the development of the required generic SOP and training materials.

By the end of 2017, countries will report on planned enrollment of over 3,200 patients on Bdq-containing treatment regimens (in at least seventeen countries) as well as over 3,400 patients on the STR (in at least seventeen countries), with CTB support under country APA3 work plans.

## **Annexes**

### ***Annex 1 Financial Report***

### ***Annex 2 Generic Implementation Planning Tool for the introduction of ND&R***



Annex 2.  
Implementation plann

### ***Annex 3 Generic Programmatic and Clinical Guide for the introduction of ND&R***



Annex 3. USAID CTB -  
Generic programmati

### ***Annex 4 Patients data***



Annex 4 Patient  
data.xlsx

### ***Annex 5 CTB supported LT-/STTA visits***



Annex 5. Additional  
TA missions.docx